

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



EH

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 231/20, 233/43	A1	(11) International Publication Number: WO 95/18094 (43) International Publication Date: 6 July 1995 (06.07.95)
(21) International Application Number: PCT/EP94/04199 (22) International Filing Date: 16 December 1994 (16.12.94) (30) Priority Data: 3875/93-7 28 December 1993 (28.12.93) CH (71) Applicant (for all designated States except US): CIBA-GEIGY AG [CH/CH]; Klybeckstrasse 141, CH-4002 Basle (CH). (72) Inventor; and (75) Inventor/Applicant (for US only): FRANCOTTE, Eric [BE/CH]; Orisstrasse 4, CH-4412 Nuglar (CH). (74) Common Representative: CIBA-GEIGY AG; Patentabteilung, Klybeckstrasse 141, CH-4002 Basle (CH).		(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i>
(54) Title: PROCESS FOR THE PREPARATION OF AN OPTICALLY PURE ENANTIOMER OF FORMOTEROL (57) Abstract The invention relates to a novel useful process for the preparation of the optically pure R,R-enantiomer of formoterol. The process is carried out by chromatographic separation on a chiral stationary phase consisting of a polysaccharide whose free hydroxyl groups are derivatised by the 4-methylbenzoyl group, and isolating the optically pure enantiomers.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Process for the preparation of an optically pure enantiomer of formoterol

The present invention relates to a novel useful process for the preparation of the optically pure R,R-enantiomer of formoterol. Formoterol: N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)phenyl]formamide and the fumarate salt of this compound, q.v. Merck Index, Eleventh Edition No. 4159, belongs to the group of the selective β_2 -sympathomimetic bronchodilators which are useful antiasthmatic drugs. Preferred suitable dosage forms are aerosols for inhalation. A known commercial product in aerosol formulation for inhalation is [®]Foradil (Ciba), which is available in numerous countries.

The pair of (R,R),(S,S)-enantiomers of formoterol and their separation into two optically pure enantiomers and two diastereoisomers are described in Chem. Pharm. Bull. 26, No.4, 1123-1129 (1978). Chirality 3:443-450 (1991) describes the enhanced activity of the R,R-enantiomer over the S,S-enantiomer. It is generally assumed of chiral beta-sympathomimetics that only one optically pure antipode of a pair of enantiomers is active. The other antipode of the pair of enantiomers is either inactive or may even cause side-effects, q.v. in this connection TiPS, June 1992 [Vol.13], pp. 231-232. The preparation of the R,R-enantiomer in high optical purity is carried out, in poor yield, by a number of complicated, and therefore expensive, synthesis steps using chiral starting materials and intermediates.

It is the object of this invention to provide a simplified, improved, and therefore more cost-effective, process for the preparation of the R,R-enantiomer of the free base of formoterol in increased yield and, in particular, in high purity of optically pure product.

Surprisingly, this object is achieved by this invention, which relates to a process for the preparation of optically pure (R,R)-N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)phenyl]formamide and the fumarate salt thereof. The process comprises separating the racemic mixture or mixture of diastereoisomers of the free compound in a mobile phase containing a nonpolar solvent and optionally a further polar protic or aprotic solvent by chromatography on a chiral stationary phase consisting of a polysaccharide whose free hydroxyl groups are derivatised by the 4-methylbenzoyl group, and optionally an inert carrier material, and isolating the optically pure R,R compound from the eluate of the mobile phase and converting said compound into the fumarate salt.

- 2 -

An essential advantage of this process resides in its combination with known cost-effective methods of preparing racemic formoterol. Racemic formoterol is prepared in per se known manner and then subjected to the novel chromatographic separation method. In one process step, the racemic mixture of formoterol is separated into the optically pure enantiomers. No troublesome synthesis of optically pure intermediates is necessary.

The terms used in the description of this invention are preferably defined as follows.

The term "optically pure" denotes in respect of a defined compound having at least one centre of chirality that said compound contains more than 95 % by weight, preferably more than 99 % by weight, most preferably more than 99.9 % by weight, of an antipode with defined configuration, e.g. according to the known rules of sequencing of Kahn, Ingold and Prelog.

The term "racemic mixture" denotes in respect of a defined compound having at least one centre of chirality a c. 1: mixture of two antipodes with defined configuration.

The term "mixture of diastereoisomers" denotes in respect of a defined compound having at least two centres of chirality a defined configuration with regard to one centre of chirality, whereas the configuration with regard to the further centre of chirality is racemic.

The term "mobile phase" defines a solvent or mixture of solvents in which the racemic mixture for separation into the optically pure antipodes, or a mixture of diastereoisomers of formoterol, is dissolved. However, an inert gas, conveniently argon, may also be used as mobile phase if the method of preparative gas chromatography is applied.

Suitable solvents for the mobile phase are mixtures of a nonpolar solvent with a polar protic or aprotic solvent.

Typical examples of nonpolar solvents are n-pentane, isooctane, petroleum ether, n-hexane, n-heptane, cyclohexane, cyclopentane, diisopropyl ether, cyclohexene, dimethoxyethane, or diethyl ether.

- 3 -

Typical examples of polar, protic or aprotic solvents are amyl alcohol, acetonitrile, isopropanol, n-propanol, n- or tert-butanol, ethanol, methanol, ethylene glycol, acetic acid or water.

It is preferred to use mixtures of a nonpolar solvent such as n-pentane, isooctane, petroleum ether, n-hexane, n-heptane, cyclohexane or cyclopentane, with a polar, protic solvent such as isopropanol or ethanol.

Mixtures of n-hexane or n-heptane with ethanol or n-hexane or n-heptane with n-isopropanol are particularly preferred.

The term "chromatographic separation" defines known methods of separating mixtures of substances which are dissolved in the mobile phase. Absorption or chemical reaction on a stationary phase establishes an equilibrium for the particular substance that causes characteristic retention times for the substance to be separated from the mixture.

Suitable known methods of chromatographic separation are typically adsorption chromatography, e.g. column chromatography or adsorption chromatography on adsorber resins, paper chromatography, thin-layer chromatography or preparative gas chromatography.

Particularly preferred separation methods are those known as HPLC (high performance liquid chromatography), and SMBA (simulated moving bed adsorption). These methods comprise using a chiral stationary phase, which consists of a polysaccharide whose free hydroxyl groups are derivatised by the 4-methylbenzoyl group. An inert carrier material can be coated with this polysaccharide.

A suitable inert carrier material for the chiral stationary phase is preferably macroporous, e.g. crosslinked polystyrene, polyacrylamide, polyacrylate, quartz, kieselgur, alumina, aluminosilicate xerogels, acidic magnesium silicate, magnesium oxide, titanium dioxide or kaolin. Silica gel is preferred.

The granular size of the inert carrier material can vary over a wide range and is typically from c. 1 μm to 1 mm, preferably from c. 1 to 300 μm . This material is porous with an average pore width of c. 1.0×10^{-8} m to 1.0×10^{-6} m.

- 4 -

The inert carrier material is coated with the derivatised polysaccharide in per se known manner, conveniently by treating the inert carrier, typically macroporous silica gel, with a solution of the derivatised polysaccharide in an organic solvent, e.g. ethanol or a mixture of methylene chloride-tetrahydrofuran, and evaporating the solvent. Numerous other methods are also known, including treatment in a fluidised-bed reactor, spraying, precipitation and the like. The macroporous silica gel can be activated beforehand by reaction with 3-aminopropyltriethoxysilane, dissolved in benzene.

The polysaccharide can be derivatised by reaction with 4-methylbenzoyl chloride. Cellulose of the [®]Avicel type (Merck) is particularly suitable.

Derivatisable polysaccharides are optically active, natural or chemically modified
polysaccharides, typically microcrystalline or native cellulose, cotton linters or cellulose from plant fibres such as cotton, flax, hemp, jute or ramie fibres.

The polysaccharide, preferably cellulose, is derivatised at 1-3, preferably 3, free hydroxyl groups by the 4-methylbenzoyl group, and can be used as coating agent for an inert carrier material or is itself used in the form of beads, q.v. published European patent application 186 133.

Suitable materials for the chiral stationary phase are known and commercially available, especially the commercial product [®]Chiralcel (Daicel) OJ, which consists of silica gel that is coated with esterified cellulose. The ester group is the 4-methylbenzoyl group.

Particularly suitable columns for chromatographic separation by HPLC are those for effecting separations on a semipreparative or preparative scale, e.g. having a diameter of 1-10 cm and a length of 20-60 cm. Particularly suitable average particle sizes of the carrier material are 10-20 µm for HPLC and 10-60 µm for SMBA.

The conversion of the free compound into its fumarate salt is carried out, if desired, in per se known manner by conventional reaction of the free compound with fumaric acid, or reaction of a sodium or potassium salt with fumaric acid or the acid chloride thereof.

The invention is illustrated by the following Examples.

Example 1: 2 g of a 2.5 % solution of racemic formoterol in hexane/ethanol (85:15 vol %) are given to a chiral CHIRALCEL OJ (Daicel Chem.Ind., Japan) HPLC column (10 x 50 cm, granular size 20 μ m). The carrier material consists of silica gel coated with p-methylbenzoyl cellulose. At a flow rate of c. 150 ml/min. and using hexane/ethanol (85:15 vol %) as mobile phase, the enantiomers are separated with a separation factor of $\alpha = 1.54$ as follows:

Optically pure fractions are obtained from 2 g of racemate and concentrated, affording 0.9 g of the first eluted enantiomer in an optical purity of ≥ 99.9 %, and 1.15 g of the second eluted enantiomer in an optical purity of ≥ 98 %. The fractions enriched with the second eluted enantiomer are chromatographed further until the optical purity is at least 99.5 %. Both fractions are additionally purified by flash chromatography. Purification is effected on silica gel (34 g, granular size 40-63 μ m, glass column 2.5 x 30 cm) in succession with mixtures of a) 250 ml of hexane/ethanol (2:1 parts by volume), b) 250 ml of hexane/ethanol (1:3 parts by volume) and c) 250 ml of hexane/ethanol (1:6 parts by volume) as mobile phases at a pressure of c. 0.2 bar. The purified fractions of the respective enantiomer are collected and then concentrated. Afterwards each residue is suspended in ether, concentrated once more and dried. The first enantiomer (0.730 g) and the second enantiomer (0.780 g) are each isolated in the form of a white powder.

To test the biological activity, each enantiomer is converted into its respective fumarate salt. This is done by dissolving 1.72 g of each optically pure enantiomer in 10 ml of methanol and adding to the solution an equimolar amount (0.29 g) of fumaric acid. After a reaction time of 1 hour at room temperature, the clear solution is concentrated at 40°C on a rotary evaporator and then dried at 40°C for 6 hours under a high vacuum. The fumarate salts are isolated as hemifumarate monohydrates and characterised:

- a) first eluted optically pure enantiomer:
(-)-(R,R)-formoterol: $[\alpha]_D = -44.7 \pm 2.3^\circ$;
- b) second eluted optically pure enantiomer:
(+)-(S,S)-formoterol: $[\alpha]_D = +47.0 \pm 0.2^\circ$.

- 6 -

Example 2: Separation of enantiomers of formoterol by simulated moving bed adsorption.

Configuration of the system:

System: Prep-SMB-System L, supplied by UOP(Universal Oil Products, Des Plaines Illinois 60017-5017, USA).

Column: 16 column (bed) system in rotary arrangement. Each column has an internal diameter of 16 mm and a length of 60 mm. The columns (vol. 0.193 ml) are filled by the slurry method. Chiral carrier material: Chiralcel® OJ, 20 µm; mobile phase: heptane-ethanol 70:30.

Separation

At a concentration of the racemate solution of 0.25 % in heptane-ethanol 70:30; a flow rate of the racemate solution of 0,52 ml/min; a flow rate of the mobile phase of 6.69 ml/min; a cycle time of 90 min; an extract rate of 3.59 ml/min; a raffinate rate of 3.62 ml/min, a productivity of 0.44 g per hour and per kg of chiral stationary phase is achieved for each enantiomer. The optical purity is 100 % for the raffinate (RR enantiomer) and 97.4% for the extract (SS enantiomer).

What is claimed is:

1. A process for the preparation of optically pure (R,R)-N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)phenyl]formamide or the fumarate salt thereof, which process comprises separating the racemic mixture or mixture of diastereoisomers of the free compound in a mobile phase containing a nonpolar solvent and optionally a further polar protic or aprotic solvent by chromatography on a chiral stationary phase consisting of a polysaccharide whose free hydroxyl groups are derivatised by the 4-methylbenzoyl group, and an inert carrier material, and isolating the optically pure R,R compound from the eluate of the mobile phase and converting said compound into the fumarate salt.

2. A process according to claim 1, which comprises separating a racemic mixture of the fumarate salt of N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)-amino)ethyl)phenyl]formamide by chromatography.
3. A process according to claim 2, which comprises separating a racemic mixture of the fumarate salt of N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)-amino)ethyl)phenyl]formamide by HPLC.
4. A process according to claim 2, which comprises separating a racemic mixture of the fumarate salt of N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)-amino)ethyl)phenyl]formamide by SMBA.
5. A process according to either claim 3 or claim 4, which comprises separating the racemic mixture in a mobile phase containing hexane or n-heptane as nonpolar solvent and ethanol as polar protic solvent.
6. A process according to claim 3, which comprises separating the racemic mixture by chromatography on a stationary phase consisting of silica gel as inert carrier coated with cellulose as polysaccharide which is derivatised by the 4-methylbenzoyl group.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/04199

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C231/20 C07C233/43

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEM. PHARM. BULL. (CPBTAL,00092363);78; VOL.26 (4); PP.1123-9, YAMANOUCHI PHARM. CO., LTD.;CENT. RES. LAB.; TOKYO; JAPAN Murase K et al 'Absolute configurations of four isomers of 3-formamido-4-hydroxy-.alp ha.-[[N-(p-methoxy-.alpha.-methylphenethyl) amino]methyl]benzyl alcohol, a potent.beta.-adrenoreceptor stimulant' cited in the application see page 1123 - page 1124 -----	1-6
A	WO,A,92 05147 (AKTIEBOLAGET ASTRA) 2 April 1992 see page 12; claims -----	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

24 February 1995

Date of mailing of the international search report

- 9. 03. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 65i epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Sánchez García, J.M.